REMARKS

Claims 27-38 were pending. Applicants have canceled claim 33 without prejudice to applicant's right to pursue the canceled subject matter in a continuation application. Applicants have amended claims 27 and 34. Support for the amendments may be found, *inter alia*, as follows: claim 27, on paragraph 9, first sentence; and claim 34, on paragraph 50, first sentence. Claims 39-50 have been added. Support for the new claims may be found, *inter alia*, in the originally-filed specification as follows: claim 39, in example 7, paragraphs 126-127; claim 40, in example 8, paragraphs 128-129; claim 41, example 9, paragraphs 130-131; claim 42, in example 10, paragraphs 132-133; claim 43, in Example 1, paragraphs 108-110, and in originally-filed claim 11; claim 44, in originally-filed claim 22; claim 45, in originally-filed claim 5; claims 46 and 47, in paragraph 10, last sentence and on page 45, line 16; claims 48 and 50, in originally-filed claim 10. Claim 49 recites the elements of claims 27, 44, 45 and 47. Entry of this amendment does not involve any issue of new matter. Applicants respectfully request entry of this amendment such that claims 27-32 and 34-50 will be pending.

Priority

The Office Action alleges that the specification as filed does not provide support for claims 33-35, which recite portions 292-330, 292-431 and 30-431 of SEQ ID NO:2, respectively. The Office Action alleges that the parent application does not recite these ranges, and concludes that these three claims are only entitled to the December 12, 2003 filing date of the instant application, rather than to the January 23, 1998 filing date of the parent application.

Applicants traverse this ground of rejection in the following grounds:

Claim 33

Claim 33 has been canceled, making the objection over the range 292-330 of SEQ ID NO:2 moot. Reconsideration of this ground of rejection is respectfully requested.

Claim 34

Claim 34 has been amended to recite residues 293-431 of SEQ ID NO:2, rather than residues 292-431 of SEQ ID NO:2. The 293-431 range corresponds to the mature form of OP-1, whose use is described in the originally-filed specification.

Paragraph 18, 3rd sentence of the specification recites as follows: "[U]seful forms of the protein include, for example, the *mature form* of the morphogen provided alone..." (emphasis added). While the specification does not explicitly state that the mature form of OP-1 spans residues 293-431 of SEQ ID NO:2, such information was known in the art at the time the application was filed. For example, U.S. Patent No. 5,266,683 (the "'683" Patent), which is referenced in the originally-filed specification, explicitly describes the 293-431 range as corresponding to the mature form of OP-1.

In the '683 Patent, the mature form of OP-1 is named OP1-18Ser as shown on column 7, lines 3-13 of its specification:

> Table I lists the various species of the hOP1 protein identified to date, including their expression sources and nomenclature and Sequence Listing references. In its native form, hOP1 expression yields an immature translation product ("hOP1-PP", where "PP" refers to "prepro form") of about 400 amino acids that subsequently is processed to yield a mature sequence of 139 amino acids ("OP1-18Ser".)

Table 1, column 8 of the '683 Patent identifies the 293-431 range as corresponding to OP1-18Ser. Specifically, the row in Table 1 labeled "OP1-18Ser" reads "Amino acid sequence of mature human OP1 protein, Seq. ID No. 1, residues 293-431." SEQ ID NO:1 in the '683 Patent and SEQ ID NO:2 in the present application are identical. Thus, the '683 Patent teaches that the mature form of OP-1 corresponds to residues 293-431 of SEQ ID NO:2.

Not only was the '683 Patent available at the time the subject application was filed, the subject application directs one skilled in the art to the '683 Patent in paragraph 69 and further incorporates its teachings by reference: "Detailed descriptions of the proteins useful in the practice of this invention, including how to make, use and test them for morphogenic activity, are disclosed in numerous publications, including U.S. Pat. Nos. **5,266,683**, 5,011,691, and/or U.S. Pat. No. 5,585,237, the disclosures of which are incorporated by reference herein." (Emphasis added). The

1st sentence of paragraph 50 of the originally-filed specification similar directs a reader to the '683 Patent: "[p]ublications disclosing these sequences, as well as their chemical and physical properties, include: OP-1 and OP-2: U.S. Pat. No. 5,011,691, U.S. Pat. No. **5,266,683**." (Emphasis added).

In sum, the specification explicitly recites the use of the mature form of OP-1, and at least one patent, cited in the originally-filed specification and incorporated by reference, describes the range of the mature form of OP-1 as residues 293-431 of SEQ ID NO:2.

Under 37 CFR 1.57, essential material may be incorporated "by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference." Since the instant specification references the '683 Patent, and since the '683 Patent explicitly discloses the range of the mature form rather than itself incorporating the range by reference, recitation of the 293-431 range in claim 34 is fully supported by the originally-filed specification.

Claim 35

The range of 30-431 in claim 35 is supported by the originally-filed specification. Paragraph 46, fourth sentence, recites: "Typically, the naturally occurring osteogenic proteins are translated as a precursor, having an N-terminal signal peptide sequence typically less than about 30 residues, followed by a 'pro' domain that is cleaved to yield the mature C-terminal domain." Therefore, if less than 30 residues are removed from OP-1, *e.g.* 29 residues, the resulting protein comprises residues 30-431 of SEQ ID NO:2. Support for the range of 30-431 in claim 35 is supported by the specification.

Additional support is found elsewhere in the specification. The specification recites the use of the morphogen comprising (i) the mature form complexed with (ii) the pro-form of OP-1. Specifically, paragraph 18, 2nd sentence, states that "Useful forms of the protein include, for example, the mature form of the morphogen provided alone **or provided in association with its precursor "pro" domain**, which is known to enhance the solubility of the protein." (Emphasis added). The mature form of OP-1 comprises residues 293-431 as explained in the preceding section under the header "claim 34." The pro-form of OP-1 spans residues 30-292 (see 2nd line in

paragraph 72 of the instant specification reciting "For example, in OP1, possible pro sequences include sequences defined by residues 30-292 (full length form)." A morphogen that comprised both a mature form (293-431) and a pro-form (30-292) of OP-1 would comprise residues 30-431, as recited in claim 35.

Based on the cancellation of claim 33 and the support identified in the sections above, applicants request that the priority of the pending claims be acknowledged as extending to the filing date of the parent application, i.e., to January 23, 1998. Reconsideration of this ground of rejection is respectfully requested.

Information Disclosure Statement

The Examiner requested that legible copies be provided of the all nonpatent references and of all non-U.S. patent references that were cited in the IDS filed February 12, 2004. Under 37 CFR 1.98(d), however, applicants are relieved of their burden to provide copies of nonpatent references and of non-U.S. patent references if the references were cited by the Examiner or provided by applicants in an IDS in an application from which the subject application claims priority under 35 U.S.C. § 120. All the requested references were either previously submitted by applicants or cited by the examiner in the parent application (Ser. No. 09/012846) from which the instant application claims priority under 35 U.S.C. § 120. Accordingly, applicants are relieved of the burden to provide the references. Applicants respectfully request that the Office obtain copies of the requested references from the parent application.

Oath and Declaration

The Office Action requests that a new Oath and Declaration be submitted on the grounds that the specification allegedly contains new matter not present in the parent application. In particular, the Office Action objects to the recitation of segments 292-330, 292-431 and 30-431 of SEQ ID NO:2 in claims 33-35. In response, applicants note that claim 33 has been canceled, and that the specification provides proper support for segments 292-431 and 30-431 as described in the preceding sections. Therefore, the application is not a continuation-in-part application, and a new

oath or declaration is not required. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Specification

The Office Action objects to the preliminary amendment filed with the application as allegedly adding new matter contrary to 35 U.S.C. §132(a). Specifically, the Office Action objects to the recitation of segments 292-330, 292-431 and 30-431 of SEQ ID NO:2 in claims 33-35. In response, applicants note that claim 33 has been canceled, and that the specification provides proper support for segments 292-431 and 30-431 as described in the preceding sections. Accordingly, the subject matter of the claims is fully supported by the originally-filed specification. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Enablement rejection under 35 USC 112

The Office Action rejects claims 29-35 under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirement.

MPEP 2164.04 states that "[i]n order to make a rejection the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." Under MPEP 2164.01(a), eight factors must be considered by an Examiner when determining whether a disclosure is enabling.

The Examiner, while properly citing the eight factors on page 5 of the Office Action, has failed to consider each of them fully when assessing enablement, and for those that are considered provides mainly conclusory statements. The rejection in the Office Action is based on two premises: first, that the specification only discloses *in vitro* examples for the effects of OP-1 on hippocampal dendrites, and second, that *in vitro* experiments cannot be extrapolated to the *in vivo* effects of OP-1 on memory formation. Both of these premises are unsupported in the Office Action.

The first premise is false because it ignores Examples 1-14 of the originally-filed specification. These examples teach in great detail, inter alia, how morphogens may be used to

increase memory in a mammal having hippocampal tissue damaged by either neurotoxins (example 7), transient global ischemia (example 8), permanent global ischemia (example 9), and traumatic brain injury (example 10). Examples 11-13 teach, inter alia, methods of assaying declarative memory in mammals treated with a morphogen, and example 14 describes, inter alia, an assay for measuring for spatial memory.

Even though these examples in the specification are prophetic, they are sufficiently detailed to allow one skilled in the art to practice the invention without undue experimentation. In fact, the Office Action itself has acknowledged that a prophetic example describing an *in vivo* experiment is sufficient to enable. On page 9, the Office Action cites to Example 18 in U.S. Patent No. 6,723,698 as anticipating the claimed invention, even though Example 18 is a prophetic example describing an *in vivo* experiment. Since a reference must be enabling to anticipate (MPEP 2121.01), the Examiner has conceded that prophetic examples are sufficient to enable the claims. (Applicants show in the next section that although enabling as a prophetic experiments for what it describes, example 18 in the '698 nevertheless fails to anticipate the pending claims for, inter alia, failing to teach all their elements).

The second premise, that *in vitro* experiments cannot be extrapolated to *in vivo* effects on memory formation, is unsupported in the Office Action. Relying on the Charron reference, the Office Action alleges that Shh and BMP *gradients* are necessary for the formation of commissural axon, and that it is unclear how the morphogens of the invention would be administered to achieve the gradients.

The Charron reference, however, is not germane to the claimed invention. The Office Action fails to provide any evidence that Shh, let alone its gradients, is required for practicing the invention. The Office Action fails to establish that (1) gradients of Shh and BMP acting during embryogenesis have any role in treating a post-embryonic mammal; (2) that gradients of Shh and BMP acting during *development* have a function in the treatment of damaged tissue; or that (3) gradients regulating axonal formation are also needed for dendritic formation.

Not only has the Office Action failed to establish any evidence for these three assumptions, the examples in paragraphs 174-179 contradict them. These examples demonstrate that contacting a culture of hippocampal neurons with OP-1 induces dendrite formation in the absence of any

exogenous Shh and in the absence of any OP-1 gradients. And even if OP-1 gradients were required for dendrite growth, which the Office Action has failed to establish, the specification teaches, as one of the modes of administration, that the morphogen may be administered intraventricularly through canuli (see example 1); canuli might be expected to create a gradient in the brain as the morphogen diffuses out of the canuli.

In sum, the Office Action has failed to apply all eight of the *Wands* factors, and instead largely relies on the Charron reference whose teachings fail to undermine the enablement of the claims. In view of the arguments set forth above, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Claim rejection under 35 USC 102(e)

The Office Action rejects claims 27-35 under 35 U.S.C. 102(e) alleging that they are anticipated by U.S. Patent No. 6,723,698 (the "698 Patent").

The Office Action alleges that examples 16.2, 17 and 18 of the '698 Patent anticipate the claimed invention. Under MPEP 2131.01, a reference must expressly or inherently describe every element of a claim to anticipate it. The '698 Patent fails to teach all the features of the pending claims and therefore it fails to anticipate them.

Examples 16.2 and 17 in the '698 Patent relate to the effects of OP-1 on the dendrite length, synapse numbers and branching of hippocampal neurons when grown in tissue culture. By contrast, claim 27 recites the following elements: (i) the administration of a morphogen to a mammal; (ii) memory formation in a mammal, and (iii) a mammal having damaged hippocampal neurons. Neither of these three elements is taught or suggested by these two examples.

Example 18 in the '698 Patent also fails to teach all the elements of the claimed invention. Example 18 relates to administering OP-1 to a rat and determining its effects on hippocampal dendrites. Although this Example teaches administration of morphogen to a mammal, the mammal has no hippocampal damage; the rat is completely normal, suffering no injury and suffering no memory dysfunction. Furthermore, this example does not teach or suggest that OP-1 has an effect on memory, nor does it teach any assay that could be performed to assay memory. In sum, Example 18

fails to teach at least two elements of clam 27.

In addition to the three examples cited, column 13, lines 1-19 of the '698 Patent is also cited in the Office Action. This section describes OP-1 fragments and variants, but is silent as to any of its uses. No recitation of any disorders or applications of the morphogens are recited in this section. This section fails to provide the missing claim elements that Examples 16.2, 17, and 18 fail to disclose.

Even if all the elements of claim 27 where taught by the '698 Patent, which they are not, the '698 Patent fails to teach the elements of several dependent claims, such as of, for example, claims 39-48. Therefore, even of the '698 Patent had anticipated claim 27, which it does not, it fails to anticipate the dependent claims. New independent claim 49 also recites additional elements that are not taught by the '698 Patent.

In view of the arguments set forth above, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Claim rejection under 35 USC 102(b)

The Office Action rejects claims 27-35 under 35 U.S.C. 102(b) alleging that they are anticipated by Withers et al. (1997).

In response, Applicants preliminarily note that the Examiner has not provided a publication date for Withers that would qualify it as a 102(b) reference. Under 35 U.S.C. § 102(b), a qualifying reference must have been published "more than one year prior to the date of the application for patent in the United States." The subject application is a divisional application of Ser No. 09/012846 filed on January 23, 1998. As explained on page 5, the subject application does not introduce any new matter, and it is entitled to the benefit of the January 23, 1998 filing date of the parent application. The Office Action has failed to show that Withers was published at least a year prior to January 23, 1997, and therefore the use of Withers as a 102(b) reference is improper.

Even if Withers were a 102(b) reference, it nevertheless fails to anticipate the claimed invention. Under MPEP 2131.01, a reference must expressly or inherently describe every element of the claim to anticipate the claim. Claim 27 recites a method of reducing memory dysfunction

associated with damaged hippocampal tissue in a mammal. By contrast, Withers relates to synapse formation in hippocampal neurons in vitro and thereby fails to teach at least three elements of claim 27. First, Wither fails to teach that the morphogens are useful in treating memory dysfunction. Second, Wither fails to teach that morphogens are useful in treating memory dysfunction *associated with damaged hippocampal tissue in a mammal.* The hippocampal neurons of Withers are not damaged. Finally, Withers fails to teach administration of a morphogen to a mammal. Instead, the morphogens of Withers are presumably added to a tissue culture dish where the cells are plated. Because Withers fails to teach at least three elements of claim 27, it cannot anticipate this claim. And even if claim 27 were anticipated by Withers, which it is not, Withers fails to teach the elements of several dependent claims such as, for example, claims 39-48, and therefore cannot anticipate these dependent claims. New independent claim 49 also recites additional elements that are not taught by Withers.

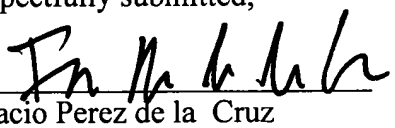
In view of the arguments set forth above, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

CONCLUSION

No fee is deemed necessary in connection with the filing of this amendment. Authorization is hereby given to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. JJJ-P02-510 from which the undersigned is authorized to draw.

Dated: August 17, 2006

Respectfully submitted,

By 

Ignacio Perez de la Cruz
Registration No.: 55,535
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant